PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : G01N 31/00	A1	(11) International Publicati n Number: WO 87/ 06343
		(43) International Publication Date: 22 October 1987 (22.10.87)

(21) International Application Number: PCT/US87/00796

(22) International Filing Date: 6 April 1987 (06.04.87)

(31) Priority Application Number: 849,758

(32) Priority Date: 9 April 1986 (09.04.86)

(33) Priority Country: US

(71) Applicant: BIONOSTICS, INC. [US/US]; Eight Craig Road, Acton, MA 01720 (US).

(72) Inventor: CHIANG, Ching ; Eight Fernwood Road, Acton, MA 01720 (US).

(74) Agents: BROOK, David, E. et al.; Hamilton, Brook, Smith & Reynolds, Two Militia Drive, Lexington, MA 02173 (US).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: MULTIPLE CONTROL STANDARD FOR BLOOD ANALYSIS

(57) Abstract

A multiple control standard for the use in the quality assurance of blood analysis instrumentation systems. The liquid control standard is able to act as a control standard for blood gas instrumentation systems measuring pH, pCO_2 and pO_2 of blood, as a control standard for a co-oximeter measuring the amount of total hemoglobin present in the blood and the relative amounts of other hemoglobin fractions present in the blood, and as a liquid control standard for ion selective electrode instrumentation systems for the measuring of electrolytes such as Na and K ions in the blood.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**ML**	Mali
AU	Australia	**GA**	Gabon	**MR**	Mauritania
BB	Barbados	**GB**	United Kingdom	**MW**	Malawi
BE	Belgium	**HU**	Hungary	**NL**	Netherlands
BG	Bulgaria	**IT**	Italy	**NO**	Norway
BJ	Benin	**JP**	Japan	**RO**	Romania
BR	Brazil	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SN**	Senegal
CH	Switzerland	**LI**	Liechtenstein	**SU**	Soviet Union
CM	Cameroon	**LK**	Sri Lanka	**TD**	Chad
DE	Germany, Federal Republic of	**LU**	Luxembourg	**TG**	Togo
DK	Denmark	**MC**	Monaco	**US**	United States of America
FI	Finland	**MG**	Madagascar		

MULTIPLE CONTROL STANDARD FOR BLOOD ANALYSIS

Background of the Invention

Clinical laboratories employ a variety of instrumentation systems for the analysis of patient samples. Frequently, three types of instruments are used to analyze particularly significant properties of fresh blood for diagnosis of respiratory-pulmonary ailments. These instruments are:

1. pH/blood gas instruments - measures blood pH, pCO_2 and pO_2.
2. Co-oximeter instruments - measures total hemoglobin, oxyhemoglobin, carboxyhemoglobin and methemoglobin.
3. ISE Electrolyte instruments - measures electrolyte (such as sodium and, potassium) content of blood.

It is common practice to employ control solutions for verifying the accuracy and reliability of these instrumentation systems. A different control solution is used for each instrument. For example, a separate and distinct control solution is used to test the blood gas analyzer. A separate and distinct control solution is used to test the co-oximeter and a third separate and distinct solution is needed to test the ion analyzer. In other words, most pH/blood gas control materials serve as controls only for pH, pCO_2 and pO_2. The blood gas controls that are formulated with hemoglobin solution or stabilized red blood cells do provide

control values for total hemoglobin in co-oximetry, but have no control values for either the other hemoglobin fractions or for electrolyte values.

Controls for hemoglobin fractions for use with co-oximetry instrumentation systems do not provide parameters for use as controls with pH/blood gas analyzers or for ISE electrolyte analyzers. Similarly, controls for ISE instrumentation are not useable for either pH/blood gas or co-oximetry instruments (in addition, some controls contain preservatives or other ingredients which make the material unsuitable for use in another type of instrument).

Summary of the Invention

This invention discloses a synthetic control solution which provides control parameters for three types of instrument systems: pH/blood gas, co-oximeters and ISE electrolytes instruments.

The synthetic liquid control is comprised of an aqueous solution buffered to a pH of from about 7.1 to 7.7 and containing sufficient bicarbonate ion to provide a pCO_2 of from about 15 to about 80 after subsequently equilibrated with the desired levels of gaseous carbon dioxide, gaseous oxygen to provide a pO_2 of from about 50 to 400, retained dyes to provide measurements of several hemoglobin fractions and salts of ions to provide measurements of these ions in solution.

Detailed Description of the Invention

This invention discloses a synthetic liquid control standard comprised of an aqueous solution buffered to a pH of from about 7.1 to about 7.7 and containing sufficient bicarbonate ion to provide a pCO_2 of from about 15 to about 80 after subsequently equilibrated with the desired levels of gaseous carbon dioxide, gaseous oxygen to provide a pO_2 of from about 50 to about 400 retained, dyes to provide measurements of total hemoglobin and of several hemoglobin fractions, sodium and potassium salts to provide measurements of these ions in solution.

In order to provide the desired pH for the respective normal, acidosis or alkalosis conditions, a buffer material should be selected which has a pK_a close to the desired working pH. A particularly useful buffer material for providing the desired pH conditions in the control solution of this invention is N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) which has a pK_a of 7.31 at 37°C. Other suitable buffer materials are, for example, N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid (TES), which has a pK_a of 7.16 at 37°C.; 3-(N-morpholino) propanesulfonic acis (MOPS), which has a pK_a of 7.01 at 37°C.; and Tri-(Hydroxymethyl) aminomethane (TRIS) which has a pK_a of 7.77 at 37°C. These and other such suitable buffer materials, including the sodium salt derivatives, are described by Good et al. Biochemistry 5, 467-77 (1966) and Ferguson et al., Analytical Biochemistry 104,

300-310 (1980), the teachings of which are hereby incorporated by reference.

The desired pCO_2 level is provided in part by addition of bicarbonate ion, for example, $NaHCO_3$, to the aqueous solution that a pCO_2 of from about 15 to about 80 is reached after subsequently equilibrated with the desired levels of gaseous carbon dioxide. The desired pO_2 level of from about 50 to about 400 is facilitated by addition of gaseous oxygen to the solution or the head space in the receptacle containing the aqueous solution. Addition of gaseous carbon dioxide similarly can facilitate maintenance of the aforesaid desired pCO_2 levels.

In a typical co-oximeter, a whole blood sample is aspirated into the instrument, mixed with diluent, hemolyzed, and brought to a constant temperature in a cuvette. A microcomputer calculates the total hemoglobin concentration present, expressed in grams per one hundred milliliters of whole blood g/dL THb. A typical co-oximeter also measures the percent oxyhemoglobin (O_2Hb), carboxyhemoglobin (COHb), methemoglbin (MetHb), and reduced hemoglobin. Each of these species of hemoglobin will absorb light at different wavelengths along the 500-650 nm range.

The control solution of the present invention contains absorbance means, such as dyes, which can absorb light in the 500-650 nm range at approximately the same percentage and wavelength as predetermined concentrations of the different hemoglobin

species. By using this control solution with the co-oximeter, it can be determined whether or not the co-oximeter is functioning properly and whether or not the instrument needs to be recalibrated.

The absorbance means need not absorb light exactly as the different species of hemoglobin do. What is important is that a relationship can be determined such that the light absorbed by the absorbance means in the control solution can be correlated to a specific absorbance level of the particular hemoglobin species in question.

In a preferred embodiment, the control solution of the present invention contains a combination of Acid Red Dye #27 (CI 16185), Acid Yellow Dye #23 (CI 19140) and Acid Blue Dye #9 (CI 42090). Also used is the combination of Ponceau 3R Red Dye (CI 16155) and Acid BLue Dye (CI 42090).

The blue dye is used because it has a maximum absorbance of light at 630nm as does methemoglobin.

The red dyes were chosen due to the fact that they show absorbance levels at the 560nm and 535nm wavelengths as does oxyhemoglobin, at the 570nm wavelength as does carboxyhemoglobin, and at the 550nm wavelength as does reduced hemoglobin. By altering the concentrations of these dyes in the control solution, the control solution can simulate samples of blood having various levels of the different fractions of hemoglobin and of total hemoglobin.

Also contained within the control solution of this invention are predetermined amounts of electrolytes for testing ISE Electrolyte instruments. These electrolytes are placed into solution with constant ionic strength by dissolving the approximate amount of the salts of these electrolytes. The electrolytes most often tested are sodium and potassium ions. Therefore, controls having a measurable range of electrolyte values of Na and K can be made by the addition of appropriate quantities of sodium and potassium salts, such as NaCl and KCl.

In a preferred embodiment of this invention, the concentration of Na ions result from the combination of the salts of the acid dyes as well as the addition of NaOH, NaCl, NaN_3 and $NaHCO_3$.

The density of the control solution can be placed at 1.01 to 1.03 and the viscosity of the solution from 2 to 4 centipoises which are similar to the density and viscosity of blood by adding up to 70 g/L of natural polymers, such as bovine serum albumin, or one of the synthetic polymers such as Polyethylene glycol (PEG) 8000, Polyvinylpyrrolidone (PVP) 40, Polyvinyl alcohol (PVA) and Ficoll 400. (Ficoll 400 is a synthetic high polymer made by the copolymerization of sucrose and epichlorohydrin produced by the Pharmacia Fine Chemicals AB Company of Uppsala, Sweden. Ficoll 400 indicates that the polymer has a molecular weight of approximately 400,000.)

To ensure a stable long shelf life of more than two years at room temperature, a chemical preservative such as sodium azide or formaldehyde can be added to the solution, or the solution can be sterilized by either membrane filtration or by high temperature sterilization if the solution does not contain the polymers used to increase the viscosity of the solution.

Two preferred formulations are listed below. By varying the concentrations of the reagents in the following formulations a varied number of control standards can be produced. These control standards will then have different levels of pH, pCO_2, pO_2, total hemoglobin fractions and concentrations of sodium and potassium ions.

Formulation I

Compound	Concentration
HEPES and/or TRIS, MOPS	20 to 100 mM
NaCl	40 to 100
KCl	2 to 8
NaOH	0 to 60
$NaHCO_3$	18 to 26
Acid Red Dye #27 (CI 16185)	2 to 5
Acid Yellow Dye #23 (CI 19140)	3 to 7
Acid Blue Dye #9 (CI 42090)	0.015 to 0.08
Polymer (PVA, Ficoll 400, PEG 8000, PVP 40 or Bovine serum albumin)	0 to 50 g/l

Formulation II

Compound	Concentration
HEPES and/or TRIS, MOPS	20 to 100 mM
NaCl	40 to 100
KCl	2 to 8
NaOH	0 to 60
$NaHCO_3$	18 to 26
NaN_3	0 to 40
Formaldehyde	0 to 60
Ponceau 3R Red Dye (CI 16155)	5 to 11
Acid Blue Dye #9 (CI 42090)	0.015 to 0.08
Polymer (PVA, Ficoll 400, PEG 8000 or Bovine serum albumin)	30 to 70 g/l

Using varying amounts of the reagents from the preferred formulations, three levels of multiple control standards can be formulated, namely Level I Control, Level II Control and Level III Control.

The multiple control standard of Level II simulates normal blood having a pH of about 7.4, a pCO_2 of about 40mm Hg and pO_2 of about 100mm Hg. The multiple control standard of Level II contains a sufficient concentration of dye to simulate a total hemoglobin concentration of about 14g/100ml of blood. This total hemoglobin reading can be produced by placing red dye, yellow dye and blue dye

into solution to give the control standard the ability to absorb the light spectrum in the wavelengths between 400 to 650nm. The yellow dye is used in order to give the control the appearance of blood but does not absorb light in the critical ranges. A preferred concentration of dyes is about 3.5mM of Acid Red Dye #27 (CI 16185), about 5mM of Acid Yellow Dye #23 (CI 19140) and about 0.04mM of Acid Blue Dye #9 (CI 42090). This concentration of dyes in solution results in a control standard having an appearance of blood and giving a total hemoglobin reading of about 14 grams in 100ml of aqueous solution as measured by the Corning 2500 Co-oximeter, 9g/100ml by the IL282 Co-oximeter and 26g/100ml by the ABL-30 Blood Gas Analyser. The multiple control standard of Level II also contains a concentration of sodium ions of about 140mM and a concentration of potassium ion of about 5mM.

The multiple control standard of Level I simulates blood having a low pH of 7.10 to 7.20, a high pCO_2 of from about 60 to 70mm Hg, and a low pO_2 of from about 50 to 65mm Hg. (This control standard thus simulates acidosis.) The control standard of Level I also contains a low concentration of Na ions from about 115 to 125mM and a low concentration of K ions from about 2.5 to 3.5mM.

The multiple control standard of Level I also contains a lower concentration of all dyes to simulate a total hemoglobin of about 9g/100ml of blood as read by the Corning 2500 Co-oximeter. A

preferred control solution of Level I contains about 2mM of Acid Red Dye #27 (CI 16185), about 3mM of Yellow Dye #23 (CI 19140), and about 0.015 mM of Acid Blue Dye #9 (CI 42090).

The multiple control standard of Level III simulates a sample of blood having a high pH of about 7.6, a low pCO_2 of about 22mm Hg and a high pO_2 level of about 150mm Hg. (This control standard thus simulates alkalosis). The multiple control standard of Level III also contains a sufficient concentration of dye to simulate a high total hemoglobin of about 18g/100ml of solution. This total hemoglobin reading is produced by having a higher concentration of all dyes, preferably about 5mM of Acid Red Dye #27 (CI 16185), about 7mM of Acid Yellow Dye #23 (CI 19149), and about 0.08mM of Acid Blue Dye #9 (CI 42090). The control standard of Level III also contains a higher concentration of sodium ions 160mM and of potassium ions of about 7mM.

The desired pCO_2 value is provided in part by the addition of bicarbonate ion, e.g. $NaHCO_3$ to the aqueous solution. CO_2 gas is then added to the acqueous solution until a pCO_2 of from about 15 to about 80mm Hg is attained, depending upon which control level is being produced.

The desired pO_2 level of from about 50 to 160mm Hg, depending upon which control level is being produced, is reached by the addition of gaseous oxygen to the solution and head space in the

receptacle containing the aqueous solution. Addition of gaseous carbon dioxide similarly can facilitate maintenance of the aforesaid desired pCO_2 levels.

The final control standard solution is retained in a sealed or air-tight receptacle such as, for example, a glass vial or ampule to retain the desired gas equilibrium. The head space in the receptacle can be filled with an appropriate gas to facilitate the provision of the aforesaid pCO_2 conditions. For example, for the acidosis blood gas control, a mixture of 65% oxygen, 5.9% of carbon dioxide and 87.6% of nitrogen is used. For the normal blood gas control a mixture of about 4.1% of carbon dioxide, 11.8% of oxygen and 84.1% of nitrogen is used. For the alkalosis blood gas control a mixture of about 2.3% of carbon dioxide, 18% of oxygen and 79.7% of nitrogen is used. It will be appreciated that any other inert gas can be used as a substitute for part or all of the nitrogen portion of the head space in the foregoing illustrative examples.

The following specific and detailed example will further illustrate the invention although it will be appreciated that this example is not meant to restrict the invention to the specific details found in such example.

EXAMPLE

The blood gas control liquids are preferably formulated to represent three levels of pH, PCO_2 and PO_2 values to have different combinations of dye concentration that simulate three levels of hemoglobin values and the visual appearance of hemolyzed blood plus three different levels of both sodium and potassium ions.

A preferred embodiment of the invention has the following formulation:

COMPOUND	CONCENTRATION
HEPES	40 mM
NaCl	40 to 100 mM
KCl	2 to 8 mM
NaOH	20 to 30 mM
$NaHCO_3$	

Three different buffers were made using HEPES, NaOH, NaCl, KCl and $NaHCO_3$ in different concentrations. They were:

	Acidosis (I)	Normal (II)	Alkalosis (III)
HEPES	40.0 mM	40.0 mM	40.0 mM
NaOH	20.0	25.7	29.6
KCl	3.0	5.0	7.0
NaCl	73.2	81.5	99.3
$NaHCO_3$	21.3	23.9	19.4

Three different levels of dyes were added to the corresponding buffer solutions.

	Acidosis (I)	Normal (II)	Alkalosis (III)
Red Dye #27	2.34 mM	3.72 mM	4.84 mM

Yellow Dye #23	1.57	2.6	3.39
Blue Dye #9	0.016	0.04	0.08

The buffered dye solutions were then separately placed in a container which was thermally controlled to 25°C. The appropriate gas mixture was then bubbled through each solution at a rate of 5 to 7 L/min. until the pH, PCO_2 and PO_2 reached equilibrium values, as determined by appropriate blood gas analyzers. The gas mixtures used had the following compositions:

	Acidosis (I)	Normal (II)	Alkalosis (III)
CO_2	6.5%	4.1%	23%
O_2	5.9	11.8	18.0
N_2	87.6	84.1	79.7

After equilibrium was reached, the gaseous solution was subdivided into 2.6 ml quantities and placed into 3ml glass ampules which had been purged with the same gas mixture used in bringing the solution to equilibrium. The filled ampules were heat-sealed.

The control liquid had an appearance of a hemoglobin solution and showed the corresponding hemoglobin value equivalents as the following table:

	THb	O_2Hb%	O_2SAT%	COHb%	MetHb%	O_2Ct	Vol%O_2
ACIDOSIS (I)							
Corning 2500	9.0g±0.5g/ 100 ml		-43±3	70±5	63±5	-5.3±0.3	
IL 282	5.5±0.5	-38±3		112±5	0.9±0.2		-2.9±0.3
Normal (II)							
Corning 2500	14.±0.5		-40±3	65±5	64±5	-7.5±0.4	
IL 282	8.8±0.5	-35±3		101±5	6.9±0.5		-4.2±0.3
Alkalosis (III)							
Corning 2500	18±0.5		-39±3	64±5	64±5	-9.4±0.4	
IL 282	11.5±0.5	-32±3		93±5	11.9±0.5		-5.0±0.3

The formulated liquid also had three levels of concentration of sodium and potassium as measured by the following different models of ion selective electrode instrumentation:

	Acidosis (I)	Normal (II)	Alkalosis (III)
Na			
Corning 902	120±3mM	140±3mM	165±4mM
614	120±3mM	140±3mM	165±4mM
Nova - 1	120±3mM	140±3mM	160±4mM
IL-501	120±3mM	140±3mM	160±4mM
K			
Corning 902	3.0±0.3mM	5.0±0.3mM	7.4±0.4mM
614	3.0±0.3mM	5.0±0.3mM	7.4±0.4mM
Nova - 1	3.0±0.3mM	5.0+0.3mM	7.0±0.4mM
IL-501	3.0±0.3mM	5.0±0.3mM	7.0±0.4mM

The ampuled formulated liquid has the corresponding values of pH, PCO_2 and PO_2 for the blood gas analyzers.

	Acidosis (I)	Normal (II)	Alkalosis (III)
pH (unit)	7.15 (7.10-7.20)	7.4 (7.38-7.42)	7.6 (7.58-7.62)
PCO_2 mm Hg	70 (66-72)	40 (38-42)	22 (20-24)
PO_2 mm Hg	60 (58-67)	102 (100-104)	150 (145-155)

Those values were measured at 37°C.

The ampules containing formulated liquid can be heat sterizilized at 15' PSI for 30 minutes for long term shelf life.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

For example, it will be understood by one having ordinary skill in the art that other dye combinations can be used which can absorb light as hemoglobin does. This invention is not limited to the illustrated examples of dye combinations.

Claims

1. A multiple liquid control standard for use in the quality assurance of blood analysis instrumentation systems, said liquid control standard being able to act as a control standard for blood gas instrumentation systems measuring pH, pCO_2 and pO_2 of blood, as a control standard for a co-oximeter measuring the amount of total hemoglobin present in the blood and the relative amounts of other hemoglobin fractions present in the blood, and as a control standard for ion selective electrode instrumentation systems measuring the concentration of electrolytes in the blood.

2. A multiple liquid control standard as recited in Claim 1, wherein the control standard is an aqueous solution buffered by a buffering agent to a pH of from about 7.1 to about 7.7 and containing sufficient bicarbonate ions to provide a pCO_2 from about 15 to about 80mm Hg, gaseous oxygen to provide a pO_2 of from about 50 to about 400mm Hg retained, absorbance means to provide a control test which corresponds to a predetermined level of hemoglobin and hemoglobin fractions, and salts of electrolytes to provide a control test for a corresponding ion selective electrode system.

3. A multiple liquid control standard as recited in Claim 2, wherein the buffering agent is selected from the group consisting of N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid, 3-(N-morpholino) propane sulfonic acid and tri-(hydroxymethyl) amino methane.

4. A multiple liquid control standard as recited in Claim 2, wherein the absorbance means is comprised of Acid Red Dye #27 (CI 16185), and Acid Blue Dye #9 (CI 42090).

5. A multiple liquid control standard as recited in Claim 2, wherein the absorbance means is comprised of Ponceau 3R Red Dye (CI 16155) and Acid Blue Dye #9 (CI 42090).

6. The liquid control standard as recited in Claim 2, wherein said liquid control standard contains a predetermined concentration of Na and K ions so that the control standard can be used to test an ion selective electrode instrumentation system which measures the amount of Na and K ions present in blood.

7. A multiple liquid control standard as recited in Claim 2, wherein the density of said control standard is about from 1.01 to 1.03 and the viscosity of said control standard is about from 2 to 4 centiposies.

8. A multiple liquid control standard as recited in Claim 7, wherein the density and the viscosity of said control standard are adjusted by a polymer selected from the group consisting of Bovine serum albumin, Polyethylene glycol 8000, Ficoll 400, Polyvinylpyrrolidone 40, and Polyvinyl alcohol.

9. A multiple liquid control standard as recited in Claim 2, wherein the pH ranges from about 7.10 to 7.20, the pCO_2 ranges from about 60 to 70mm Hg, the pO_2 ranges from about 50 to about 65mm Hg, the Na ion concentration ranges from about 115 to about 125 mM, the K ion concentration ranges from about 2.5 to about 3.5 mM and the absorbance means simulates blood having a low level of total hemoglobin.

10. A multiple liquid control standard as recited in Claim 9, wherein the absorbance means is comprised of Acid Red Dye #27 (CI 16185) and Acid Blue Dye #9 (CI 42090).

11. A multiple liquid control standard as recited in Claim 9, wherein the absorbance means is comprised of Ponceau Red Dye 3R (CI 16155) and Acid Blue Dye #9 (CI 42090).

12. A multiple liquid control standard as recited in Claim 2, wherein the pH ranges from about

7.35 to 7.45, the pCO_2 ranges from about 35 to 45mm Hg, the pO_2 ranges from about 95 to about 110mm Hg, the Na ion concentration ranges from about 135 to about 145 mM, the K ion concentration ranges from about 4.5 to about 5.5 mM and the absorbance means simulates blood having a normal level of total hemoglobin.

13. A multiple liquid control standard as recited in Claim 12, wherein the absorbance means is comprised of Acid Red Dye #27 (CI 16185) and Acid Blue Dye #9 (CI 42090).

14. A multiple liquid control standard as recited in Claim 12, wherein the absorbance means is comprised of Ponceau Red Dye 3R (CI 16155) and Acid Blue Dye #9 (CI 42090).

15. A multiple liquid control standard as recited in Claim 2, wherein the pH ranges from about 7.55 to 7.65, the pCO_2 ranges from about 15 to 25mm Hg, the pO_2 ranges from about 140 to about 160mm Hg, the Na ion concentration ranges from about 150 to about 170 mM, the K ion concentration ranges from about 6.5 to about 7.5 mM and the absorbance means simulates blood having a high level of total hemoglobin.

16. A multiple liquid control standard as recited in Claim 15, wherein the absorbance means is

comprised of Acid Red Dye #27 (CI 16185) and Acid Blue Dye #9 (CI 42090).

17. A multiple liquid control standard as recited in Claim 15, wherein the absorbance means is comprised of Ponceau Red Dye 3R (CI 16155) and Acid Blue Dye #9 (CI 42090).

18. A multiple control standard for use in the quality assurance of blood analysis instrumentation systems, said liquid control standard being able to act as a control standard for blood gas instrumentation systems measuring pH, pCO_2 and pO_2 of blood, as a control standard for a co-oximeter measuring the amount of total hemoglobin present in the blood and the relative amounts of other hemoglobin fractions present in the blood, and a control standard for ion selective electrode instrumentation systems measuring the concentration of Na and K ions in the blood, wherein the control standard is an aqueous solution buffered by a buffering agent to a pH of from about 7.1 to about 7.7 and containing sufficient bicarbonate ion to provide a pCO_2 from about 15 to about 80mm Hg, gaseous oxygen to provide a pO_2 of from about 50 to about 400mm Hg retained, absorbance means to provide a control test which corresponds to a predetermined level of hemoglobin and

hemoglobin fractions, said absorbance means being comprised of Acid Red Dye #27 (CI 16185) and Acid Blue Dye #9 (CI 42090), and salts of Na and K to provide a control test for a corresponding ion selective electrode instrumentation system.

19. A multiple control standard for use in the quality assurance of blood analysis instrumentation systems, said liquid control standard being able to act as a control standard for blood gas instrumentation systems measuring pH, pCO_2 and pO_2 of blood, as a control standard for a co-oximeter measuring the amount of total hemoglobin present in the blood and the relative amounts of other hemoglobin fractions present in the blood, and a control standard for ion selective electrode instrumentation systems measuring the concentration of Na and K ions in the blood, wherein the control standard is an aqueous solution buffered by a buffering agent to a pH of from about 7.1 to about 7.7 and containing sufficient bicarbonate ion to provide a pCO_2 from about 15 to about 80mm Hg, gaseous oxygen to provide a pO_2 of from about 50 to about 400mm Hg retained, absorbance means to provide a control test which corresponds to a predetermined level of hemoglobin and hemoglobin fractions, said absorbance means being comprised of Ponceau 3R Red Dye (CI 16155) and Acid Blue Dye #9 (CI 42090).

INTERNATIONAL SEARCH REPORT

International Application No PCT/US87/00796

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC: GOIN/3100 ; US: 436/11

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
US	436/11-18

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	US,A, 4,485,174, Published 27 Nov. 1984, (Chiang et al.)	1-19
A	US,A, 4,469,792, Published 04 Sept. 1984, (Simmonds et al.)	1-19
A	US,A, 4,458,021, Published 03 July 1984, (Herring.)	1-19
A	US,A, 4,163,734, Published 07 Aug. 1979, (Sorensen et al.)	1-19
Y	US,A, 4,279,775, Published 21 July 1981, (Louderback et al.).	1-19
Y	US,A, 4,369,127, Published 18 Jan. 1983, (Cormier et al.).	1-19

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [3]	Date of Mailing of this International Search Report [3]
26 June 1987	10 JUL 1987
International Searching Authority [1]	**Signature of Authorized Officer** [20]
ISA/US	T. J. Wallen